Date: July 5, 2009

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Sponsor: Dendreon Corporation
Meeting type: C
Meeting category: other BLA
Meeting date & time: June 5, 2009, 3-4:30 pm
Meeting format: face-to-face
Meeting Chair/Recorder: Lori Tull, RAC

Attendees

FDA:
Ashok Batra, MD
Kimberly Benton, PhD
Peter Bross, MD
Tom Finn, PhD
Bindu George, PhD
Syed Husain, PhD
Malcolm Moos, PhD
Raj Puri, MD, PhD
Lori Tull, RAC
Gang Wang, PhD
Celia Witten, MD, PhD
Keith Wonnacott, PhD
Bo Zhen, PhD
Ghanshyam Gupta, PhD
Rick Wilson
Aileen Buckler
Craig Zinderman
Bhanu Kannan

Dendreon:
Mary Coon (Quality)
Alison Del Vento (Medical Affairs)
Mark Frolich (Clinical and Medical Affairs)
Heidi Hagen (Supply Operations
Helen Kim (Regulatory Affairs)
Karen Krstulich (Regulatory Affairs)
Nicole Provost (Product Development)
Elizabeth Smith (Regulatory Affairs)
Robert Sims (Clinical Affairs)
Connie Spooner (Regulatory Affairs)
Frances Stewart (Biostatistics)
David Urdal (Senior Management)
Yi Xu (Biometrics)
Brent Blumenstein (Biostatistics consultant)

Background and Objectives

This meeting was requested by the sponsor on April 16, 2009 to discuss the final results of D9902B and the proposed content and format of a complete response to the 5/8/07 CR letter. The information package was submitted on, 2009. FDA draft comments were transmitted to the sponsor on June 4, 2009.

Discussion

1. Dendreon proposes to submit the D9902B and PB01 CSRs (including datasets, case report forms (CRFs), etc.) in August 2009. The remaining CTD components, including the Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Pharmacology, Summary of Clinical Safety, and proposed labeling will be submitted in October 2009. Is this acceptable?

FDA Response

Yes, this is acceptable.

We request that all the protocols and the amendments and a sample blank consent form used during the study be included in the study report. Please see Bioresearch Monitoring (BIMO) additional comments for additional requests.

Sponsor Response: Dendreon responded that they would submit the requested information.

2. The primary efficacy and safety database for the D9902B and PB01 CSRs will have a data cut-off of January 18, 2009. The Safety Update will include any remaining survival and safety data from D9902B not included in the CSR, as well as safety data from all other ongoing studies. Is this acceptable? We also wish to discuss the timing of the data cut-off for and submission of the Safety Update.

FDA Response

Yes this is acceptable. We can discuss timing of the safety update.

Summary of Discussion: Dendreon noted that the proposed data cut-off would be July 31, 2009, but there would be limited amount of new clinical data at that time. CBER responded that Dendreon could submit the safety update earlier than February and possibly as early as December.

3. As requested, a list of the variables proposed for the efficacy dataset for Study D9902B as well as relevant information from the Study PB01 database is included in the briefing document. The indicated key demographic and stratification variables will be included in all analysis datasets of D9902B. Are these acceptable?

FDA Response

Yes, this is acceptable.

4. For the secondary endpoint of time to objective disease progression in Study D9902B, Dendreon proposes to provide patient scans only upon request. Is this acceptable?

FDA Response

Yes, this is acceptable.

5. Does the Agency agree that the proposed analysis plan and proposed format/content for the Safety Update (described in the meeting briefing document) are acceptable?

FDA Response

Yes, this is acceptable.

Status of Responses to the May 8, 2007 Complete Response Letter

6. Dendreon has provided responses to Items 1 – 7 (CMC) of the Complete Response letter. The briefing document contains a listing of past BLA submissions relating to these items. Does the Agency agree that the responses to Items 1 – 7 are complete?

FDA Response

The Agency cannot provide official comment on the adequacy of the supplied responses provided in BLA amendments until all items in the Complete Response letter are addressed. BLA amendments are reviewed when submitted and are still being evaluated. At this time we offer the following comments:

a. Letter item #1:

   i. Process validation for GMP modules: The aseptic process validation study appears to be adequate to support [redacted] workstations in [redacted] modules. We note you have plans to expand your Morris Plains Facility by adding additional manufacturing [redacted] different layout. Please be advised that the [redacted] may need to be validated and a new facility inspection may be needed. Future process validation, including the new [redacted], should be conducted at the full throughput of the intended manufacturing level.

Summary of Discussion: Dendreon confirmed that they intend to do complete validation of the additional manufacturing modules planned for the New Jersey manufacturing facility, and they understand that the expansion may require inspection. Dendreon explained that the new [redacted] scheduled to come into [redacted] to support the initial launch of sipuleucel-T. At the time of the anticipated inspection of the current to-be-licensed facility, the [redacted] space will be completed, with some equipment in place, but the [redacted] will not be fully qualified, and therefore not in use. Further discussion of the NJ plant expansion ensued; refer to slides 1 and 2. Dendreon confirmed that the existing [redacted] workstations (WS) will not be taken off line during the construction of the expansion, because a hard separation wall will be in place until all validation and required environmental monitoring is completed. Regarding the Agency's

comment that future process validation should be conducted at full throughput of the intended manufacturing level, Dendreon noted that the qualification study that was performed for the [redacted] WS facility will not be feasible with [redacted] WS, due to a number of reasons, including the quantity of normal donor aphereses that would be required. Dendreon proposed to have further discussion of the validation of the additional [redacted] WS at a later time.

ii. Insufficient personnel for aseptic process validation: The provided information on new personnel and training is adequate. Please also comment on the training of potential new hires for the [redacted] intended shifts of personnel for the NJ facility.

Sponsor Response: Dendreon responded that they have a well-established training program in place for new hires. Dendreon showed an illustration of the 3-step program on slide 3.

iii. Product tracking in the QC lab:

1. Tracking samples in the QC lab: The provided documentation appears to adequately address our concerns. However, new SOPs, forms, software, computer workstations, and additional equipment have been implemented in the QC lab and these changes are being evaluated carefully.

2. Lack of bar code reader in QC lab: Your plans to implement a bar code reader appear to address our concerns. You have indicated that the QC lab now has 10 LIMS workstations each with a barcode reader and sample tubes contain barcodes. It is not clear at which stages barcodes are scanned during the testing process. Please also provide more information on the LIMS Operational and Performance Qualification validation study.

Sponsor Response: Dendreon will submit a summary of the validation (OQ and PQ) performed for LIMS in an upcoming BLA amendment. It was agreed that any additional questions about bar code readers in the QC lab can be resolved at the pre-licensing inspection.

b. Letter item #2- Shelf life of [redacted]: The provided data appear to adequately address our concerns.

c. Letter item #3- Shipping validation: The provided information to date does not adequately resolve this issue. Please provide the results from the planned shipping validation study from the NJ facility. We also note that [redacted] lots were manufactured at the NJ facility. In addition to the line listing of product testing already provided, please provide shipping information on these lots. It is not clear if these lots were represented in the shipping information provided in Amendment 16.

Sponsor Response: Dendreon will provide the results of the shipping study in the upcoming BLA amendment. Regarding the [redacted] lots manufactured for Study D9902B at the NJ facility, as listed in BLA Amendment 027, Dendreon confirmed that this includes lots in addition to those provided in Amendment 16. The upcoming amendment will provide shipping information for all additional D9902B lots.

d. Letter item #4- Shipping and handling:

i. Manufacturing step time for formulation: Based on your recent process validation study you have set as a step time [redacted] for this manufacturing step. Please comment on how implementation of this step time impacts past logistical estimates and future scheduling procedures. Please also note that appropriateness of this step time will depend upon results from your planned [redacted] stability study.

Sponsor Response: Dendreon confirmed that the [redacted] step time ([redacted]) is commensurate with their past experience and is already incorporated into their procedures. Thus it will have no impact on logistical and scheduling procedures. [redacted] stability study results will be included in the upcoming BLA amendment

ii. Provide data demonstrating that the 18 hour shelf life is sufficient: The provided logistical information partially addresses our concerns; however, it is still not clear if 18 hours will be adequate to ship product to distant clinical sites within normal business hours:

1. Results from the planned shipping validation study would be very helpful to address this issue. Please provide results from this study when available. The example logistical information for scheduled delivery at distant points throughout the continental U.S. is helpful, but given the short shelf life, potential delays due to weather or traffic conditions, time zone changes, and limitations in delivering during normal business hours it is difficult to assess the value of this information.

2. In Amendment 016 you provided shipping times for the APH and final product for [redacted] lots of sipuleucel-T/placebo and [redacted] lots of APC8015F produced and shipped from the Morris Plains, NJ facility. None of these shipments were made to the west coast so it is not clear if the product can be delivered during normal business hours to these locations.

Sponsor Response: Dendreon reviewed the purpose of the current NJ shipping study, to clarify that this study is designed to demonstrate that the sipuleucel-T shipper maintains proper storage conditions even if the shipper is exposed to extreme conditions during actual shipment. Regarding CBER's comments on unforeseen delays during shipment,

Dendreon cited extensive experience with logistics while shipping more than [redacted] lots of clinical material over the years. Dendreon will gain experience in shipping from NJ to the west coast as part of the planned open-label study; data related to that experience can be reviewed at the pre-licensing inspection.

3. For your ongoing phase II P07-1 and P07-2 studies you argued that it was not in the best interest of the patient to include as part of the 18 hour shelf life the time required to complete infusion of the product, as this might lead to situations where infusion is rushed in order to meet this requirement. We agree that rushing an infusion procedure should be avoided. One of the key logistical challenges for this product is delivering the final product for infusion during normal business hours. Please comment on the timing of delivery of this product with respect to remaining business hours to ensure that infusions will not be rushed.

Sponsor Response: Dendreon explained that for sipuleucel-T, "business hours" are not a set timeperiod (e.g., 9 am to 5 pm), but rather are defined by each treating physician. Dendreon works through those requirements as they develop their relationship with the physicians, and their requirements are incorporated into the scheduling processes. CBER noted that it would be informative to see data on the shipping of actual product from NJ to other distant locations, with information on how much of the shelf life time is left for product infusion.

4. Some questions still remain as to how QC product testing will be prioritized depending on changing scheduling conditions. We recommend that in order to ensure that QC testing is not rushed that an adequate amount of time is allotted to perform lot release testing of all manufactured lots regardless of manufacturing schedule. The amount of time allotted should be based on manufacturing experience and results from your [redacted] workstation process validation study.

Sponsor Response: Dendreon agreed that it is important to allot adequate time for QC testing, however they prefer not to set strict time limits for the various tests. Dendreon's general practices and business rules are designed to accommodate delays or other schedule changes while taking into account the time required for QC testing. The Agency confirmed that time limits are not required, but that information on applicable procedures or business rules would be helpful. Dendreon agreed to make them available at inspection.

5. Upon inspection you described that a Shop Floor Manager would be in charge of overseeing production schedules and would work closely with the Scheduling group in Seattle, the Plant Manager, and the QC manager. Please provide updated information on oversight of manufacturing logistics.

Sponsor Response: Dendreon will provide updated information on the oversight of manufacturing logistics in the upcoming BLA amendment.

e. Letter item #5- Comparability of manufacturing data between NJ and other sites: The provided data from each site appears comparable and addresses our concerns.

f. Letter item #6- Equivalency of [redacted] sterility testing to CFR method:

i. Clarify where previous studies were performed and differences between instruments used: The information provided appears adequate.

ii. Sponsor stated in BLA they would conduct additional studies: the results from the additional equivalency study documented in BLA Amendment #027 appear to be adequate, however we are still evaluating the design of this study and the results obtained.

iii. Use of [redacted] for [redacted]: The information provided is adequate.

g. Letter item #7- Test method validation studies:

i. [redacted]: The information provided appears to be adequate.

ii. Gram stain: The information provided appears to be adequate.

iii. [redacted]: The information provided appears to be adequate.

7. Regarding Item 8 of the Complete Response Letter, does the Agency agree that the results from Study D9902B will address the Agency's request for additional clinical data to support the proposed efficacy claim for the treatment of men with metastatic castrate resistant prostate cancer?

FDA Response

The proposed submission appears likely to address the request for additional data. Licensure decisions will depend on the review of the submitted data.

8. Items 9 and 10 of the Complete Response letter will be addressed through a pharmacovigilence plan as summarized in the briefing document. We are seeking early input with regard to the design of the proposed plan. Does the Agency agree with Dendreon's approach?

FDA Response

1. We have only preliminary comments on the PVP thus far, based on initial review of materials presented in the pre-BLA meeting package.

2. The proposed registry approach to clarification of safety and efficacy in African Americans may be reasonable but will require close consideration of the clinical trial safety data and the plans for registry data collection and analysis in the final BLA submission. For example, what measures would control for potential confounding factors, such as possible differences between African American and other patients in the stage of disease at enrollment?

Summary of Discussion: The proposed pharmacovigilance plan and patient registry will be better discussed after CBER reviews a more complete draft version of the plan. CBER indicated that they are very interested in starting a dialogue regarding the proposed pharmacovigilance plan and registry early. Dendreon agreed to submit a draft, formatted in accordance with ICH Guidance E2E, Pharmacovigilance Planning, prior to the submission of the D9902B CSR. Dendreon noted that they understand the Agency's concerns about confounding factors in the African American registry approach and will try to collect baseline data on important prognostic factors.

3. Regulations require submission of accumulating safety data **quarterly** for the first three years after a new product's licensure.

Sponsor Response: Dendreon confirmed that they plan to submit safety data on the required quarterly schedule.

9. As noted in Item 11 of the Complete Response letter, the Agency considers the PA2024 protein to be an active ingredient, rather than a raw material, used in the manufacture of sipuleucel-T. The rationale for considering PA2024 to be a raw material is provided in the briefing document. Does the Agency agree with Dendreon's assessment?

FDA Response

No, we do not agree with your rationale for considering PA2024 protein to be a raw material rather than an active ingredient. The information provided to the BLA to date supports that PA2024 fits the definitions in both the ICH Q7 guideline which you cited, and in 21 CFR 210.3(b)(7):

> *"Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product in a modified form intended to furnish the specified activity or effect."

Please clarify your specific concerns with stating in the BLA and proposed labeling that PA2024 is an active ingredient.

Summary of Discussion:

Dendreon cited specific concerns related to labeling the PA2024 protein as an active pharmaceutical ingredient (API) in sipuleucel-T. CBER expressed their views in support of the API designation, indicating that the protein does satisfy the definition in 21 CFR 210.3(b)(7) in that PAP could be viewed as the active immunogen and the rest of the components are there to amplify the immune response. Furthermore, describing the product as antigen presenting cells [without citing the PAP specificity] does not distinguish it from similar products. In the future, if a new impurity appears and provoked an anti-self response, there could be a safety concern. CBER assured Dendreon that they do not intend to impose additional testing requirements for PA2024 with designation as an active ingredient. CBER expressed interest in further discussions with Dendreon on creative ways to deal with the issue in the Labeling, and noted as example that instead of quantifying the material in the final product, Dendreon might refer to the starting quantity or ratio of protein to cells in the [redacted]. It was agreed that this topic would be discussed again prior to the submission of draft labeling planned for October 2009.

10. Please note the proposed submission schedule and planned updates to the BLA. Please advise on the timing of the start of the review clock for the Class 2 Resubmission of BLA STN 125197/0. Specifically, will submission of all the updated CTD components (i.e., Clinical Overview, Summaries of Clinical Pharmacology, Safety, and Efficacy, proposed labeling, etc.) be necessary for CBER to consider the "response complete" for purposes of a new PDUFA review clock?

FDA Response

The response will be considered complete when responses to all items of the complete response letter have been submitted.

Summary of Discussion: Dendreon summarized and CBER concurred with the agreed-upon submission schedule: several CMC items in July 2009, the D9902B CSR in August, summaries and labeling in October 2009, with the PDUFA clock starting when the last submission is completed in October 2009. In response to Dendreon's question about a 74-day review letter, CBER stated that a 'resubmission acknowledgement' letter would be issued on a shorter time frame. FDA will provide more details as a follow-up to this meeting.

Additional Comments/Recommendations:
Clinical

1. In your CSR for PB01 please include some estimate of effects of APC 8015F on overall survival as well as a sensitivity analysis for possible APC 8015F effects on overall survival in your Integrated Summary of Efficacy report.

Sponsor Response: Dendreon will include exploratory analyses of the effect of APC8015F on overall survival in the D9902B CSR, as well as the Summary of Clinical

Efficacy. Survival follow-up for PB01 subjects was comprehensively collected in D9902B rather than PB01, so survival analyses for PB01 will be included in the D9902B CSR rather than the PB01 CSR, which will focus primarily on safety. Analyses will include descriptive statistics of 3 subject groupings, i.e., those who received sipuleucel-T, those who received salvage therapy, and those placebo subjects who did not participate in the cross-over study. In addition, time dependent covariate analyses which include in the model treatment, baseline covariates, and time to treatment with APC8015F may be provided.

2. Please include sensitivity analyses for OS adjusted for:

    a. Prior Docetaxel use (15.5% in Sip-T arm and 12.3% in the Control arm received upfront Docetaxel) and Chemotherapy use (19.6% Sip and 15.2% Control) to evaluate potential confounding effect of the imbalance in pre-treatment Docetaxel therapies in the sipuluecel-T vs placebo arm.
    b. Bone and Soft tissue determine the potential confounding effect of the imbalance in the baseline characteristics in the sipuleucel-T arm vs. the placebo arm (41.9% sipuleucel-T vs. 48.5% Placebo arm)

3. We note that a sensitivity analysis for use of Docetaxel has been performed, however we would like to evaluate potential effects which might be related to imbalances resulting from delays docetaxel therapy and imbalances in dose of Docetaxel in the salvage therapy arm, the arm that did not receive salvage therapy within the placebo group and the treatment arm of Study D9902B. Please propose a sensitivity analysis plan to evaluate the impact of the timing, number of cycles of Docetaxel administered, and the number of subjects who received post-study Docetaxel therapy after ODP on the overall survival of the study subjects.

Sponsor Response: Dendreon will provide survival analyses adjusting for individual baseline covariates, including use of any chemotherapy, use of docetaxel, and localization of disease. Preliminary results indicated that the treatment effect remains consistent following adjustment, and that none of these factors are treatment effect modifiers. The treatment effect also appears to be consistent following adjustment for multiple baseline covariates. Dendreon clarified that some of the specific docetaxel information requested by the Agency is not available, since data are limited to the information collected on the case report forms, the purpose of which was to collect survival information, and which therefore did not include the number of cycles or cumulative doses of chemotherapy after objective disease progression. Dendreon noted that they have a robust collection of baseline prognostic factors, but beyond that, the prognostic factor data are less complete. Dendreon has worked on models to approach this issue, as described in slides 4 and 5, recognizing that many other models are possible. Dendreon reiterated that suggestions from FDA for approaching these analyses would be welcome. The Agency stated that they are very open to discussing alternative approaches to these types of exploratory analyses.

BIMO

1. Please describe your study site clinical monitoring procedures used during the study regarding the study conduct to ensure that the clinical investigator was complying with the human subject protection and protocol requirements. If a third party was used to monitor the study please identify the third party. We request the procedures to include but not limited to (i) the frequency of monitoring; (ii) the monitoring procedures including the type of documents monitored and verified; and (iii) the procedures performed to correct deficiencies, if any.

2. Please include any additional sponsor required obligations to be fulfilled by the investigator regarding the study conduct, if applicable. Please include a blank form and any procedures instituted during the study to document the roles and responsibilities of study personnel.

3. Please include the name and address including the telephone number of the clinical investigator responsible for the study in the BLA submission. In order to facilitate BIMO review, we request that you include the number of subjects enrolled at each site. Also, if the clinical investigator has left the institution please identify the current investigator responsible for the study conduct in order for FDA to communicate and conduct an inspection in a timely manner.

4. Please identify satellite sites, if any and applicable, with the address and telephone number.

5. Please include the name and address of the Institutional Review Board (IRB) responsible for the study at each study site. Please identify local IRBs, if any and applicable.

6. Please include a table listing the protocol deviations, if any, with the site and the subjects identified.

Additional Discussion:

Pre-license Inspection: It was agreed that, with the October 2009 (final) submission, Dendreon will provide information on any changes at the NJ facility, including equipment qualification as well as a summary of environmental monitoring data since the last inspection. If the final submission is to be in late October 2009, it is very likely that the inspection will be scheduled for January of 2010. The Agency has no plan at this time to inspect Diosynth or other contract manufacturers.

Advisory Committee Potential: The Agency cannot comment on whether an Advisory Committee will be necessary prior to submitting the results from D9902B. If an Advisory Committee is deemed necessary, the Agency will inform Dendreon as soon as possible.

Interim Analysis: Dendreon confirmed that the BLA resubmission will include the open and the closed minutes from the IDMC meetings. Dendreon also reiterated that it was highly unlikely that release of the interim results had an impact on the interpretability of the final results. The interim results were released in October 2008, and the 304th death event was in November 2008.

Manufacturing Expansions: Dendreon is planning a very controlled stepwise launch, but expressed the importance to get the product out to patients as soon as possible. Manufacturing capacity with [redacted] WS and [redacted] WS was discussed. [redacted]

General Discussion:

1. In response to the Agency's question, Dendreon noted that they had a preliminary meeting with CMS approximately 2 years ago, because the demographics of the sipuleucel-T patient population would qualify most patients for Medicare. Serious discussions with CMS will not take place without an approved final product label.

2. Dendreon confirmed that the labeling information will be submitted per SPL requirements.

3. The Agency's question about new information from immune monitoring led to a discussion of some exploratory studies of the changes observed in patient cells following the first (Week 0) treatment. The data set is too small to draw any clinical conclusions. It was agreed, however, that Dendreon would include a discussion of recent product characterization findings in an upcoming BLA amendment.

4. The Agency asked about the ordering process for the product, procedures for noninfusable product, and other investigator obligations that were part of the clinical study. This information (as relates to the clinical study, since the ordering process will be different commercially) will be included with submission of the D9902B CSR.

5. In response to the Agency's question about differences between fresh (sipuleucel-T) product and frozen (APC8015F) product used in the salvage study, Dendreon presented data from the salvage study showing [redacted]) The immune monitoring data are currently being analyzed, such as the [redacted] response shown in slide 8.

6. Regarding the open label clinical trial P09-1, Dendreon reported that the protocol is currently being submitted to IRBs and the first patient is expected to be enrolled in July 2009. Approximately 40 subjects who were randomized to placebo in the D9902B study will have the opportunity to enroll first, and as space becomes available the trial will be opened to other subjects with metastatic castrate resistant prostate cancer.

Chronology
Meeting Minutes Drafted/Tull:6/18/09
Meeting Minutes Finalized/Tull: 7/5/09